Remarks

Claims 1-28 are pending in this Application. Claims 1-7 and 9-13 are allowed. The Examiner is thanked for stating that Claims 1-7 and 9-13 have allowable subject matter and indicating that these claims have not been described or patented in any prior art.

In the Office Action mailed October 6, 2004, the Examiner:

1. Rejected Claims 8 and 18 under 35 U.S.C. § 112 for including a limitation with insufficient antecendent basis;
2. Rejected Claims 20, 26, and 27 under 35 U.S.C. § 102(b) for being anticipated by Goux (US Patent No. 5,302,520);
3. Rejected Claims 14, 15, and 18 under 35 U.S.C. § 103(a) as being unpatentable over Landau et al. in view of Schneider (US Patent No. 6,764,817); and
4. Objected to Claims 16, 17, 21-25 and 28 for depending upon a rejected base claim.

Applicants respectfully address the basis for each of the Examiner's rejections and objections below.

Claims Rejection – 35 U.S.C. § 112 – Claims 8 and 18

On page 2 of the Office Action, the Examiner rejected Claims 8 and 18 under 35 U.S.C. § 112. The Office Action states that Claims 8 and 18 recite the limitation "the flux," for which there is insufficient antecendent basis. Applicants hereby respectfully submit amdended Claims 8 and 18, amended to describe the analyte as "selected from the group consisting of pyruvic acid, acetic acid citric acid, isocitric acid, cis-aconitic acid, 2-ketoglutaric acid, succinic acid, fumaric acid, malic acid, oxaloacetic acid, and mixtures thereof." Support for amended Claims 8 and 18 can be found throughout the Specification, examples of which are shown below:

> [0007] The present invention provides a combination of carbon-13 and deuterium metabolic tracers and methods that <u>when used in conjuction with nuclear manegtic resonance spectroscopy, provide a measurement of metabolic fluxes in the target organisms</u>. [Emphasis added]

[0031] The fraction of [1,6-$^{13}C_2$] glucose in plasma glucose was calculated as *fg*. The values measured in spectra collected at 120, 150 and 180 min were averaged for each subject and used in the calculation of GP. The rate of appearance of glucose (R_a) was calculated from the known infusion rate of [1,6-$^{13}C_2$]glucose, *r*, divided by the average fraction found in plasma over the 120-180 min period. Glucose production is then defined as R_a minus the rate of infusion of [1,6-$^{13}C_2$]glucose, or GP = (*r*/*fg*) – *r*.

The fraction of glucose derived from glycogen, PEP and gluconeogenesis was estimated from the ratio of deuterium enrichment at positions 2, 5 and 6*S* as reported in the ^{2}H NMR spectrum of monoacetone glucose (42) using the following equations:

Glucose fraction from glycogen = 1 - (H5 / H2) (1)
Glucose fraction from glycerol = (H5 - H6*S*) / H2 (2)
Glucose fraction from PEP = H6*S* / H2 (3)

Relative anaplerotic flux (OAA → PEP), pyruvate recycling flux (PEP → pyruvate or equivalent pathway), and gluconeogenic flux (PEP → glucose) were calculated from the multiplet areas measured in the ^{13}C NMR spectrum of urinary glucuronate or phenylacetylglutamine as described previously. For urinary glucuronate C5 (the C5β resonance was analyzed) the relevant equations are:

OAA → PEP = (C5D56 – C5D45)/C5D45 (4)
PEP → pyruvate = (C5D56 – C5Q)/C5D45 (5)
PEP → glucose = (C5Q – C5D45)/C5D45 (6)

For phenylacetylglutamine C2 the relevant equations are:

OAA → PEP = (C2D23 – C2D12)/C2D12 (7)
PEP → pyruvate = (C2D23 – C2Q)/C2D12 (8)
PEP → glucose = (C2Q – C2D12)/C2D12 (9)

[Emphasis added]

With the paragraphs shown above, amended Claims 8 and 18 are believed to be adequately supported by the disclosure. Applicant respectfully requests entry and allowance of amended Claims 8 and 18.

Claims Rejection – 35 U.S.C. § 102(b) – Claims 20, 26, and 27

In page 2 of the Office Action, the Examiner rejected Claims 20, 26, and 27 under 35 U.S.C. § 102(b) for being anticipated by Goux. The Office Action states:

> Goux teaches a method of enzymatic synthesis of isotopically labeled carbohydrates and sugars. Labeled citric acid cycle (Krebs cycle) intermediates may be rapidly and conveniently synthesized from labeled

> pyruvate, lactate or alanine. See abstract. The labeling is done with isotopic ^{13}C and is measured via nuclear magnetic resonance. See Example 7. While not expressly disclosed in Goux, the determination of the rate of gluconeogenesis is inherent because the rate of production of the intermediates can be used as an estimate.

Applicants strongly disagree that determining the rate of gluconeogenesis is inherent in Goux. As determined in *In re Oelrich*, to be inherent, the missing descriptive matter (determination of the rate of gluconeogenesis) must be necessarily present in the enzymatic synthesis of isotopically labeled carbohydrates as described by Goux and must be recognized by one of ordinary skill. [*In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981), see MPEP 2112]. Applicants submit that determining a rate of gluconeogenesis does not necessarily flow from the teachings of Goux of a method of enzymatic synthesis of a labeled carbohydrate and method of preparing a labeled carbohydrate. In fact, Goux teaches that enzymatic synthesis requires a number of steps, and independent or combined, none of the steps teach or necessarily present a determination of the rate of gluconeogenesis. When Goux describes the use of nuclear magnetic resonance, it is only described as a means for measuring the overall yield of enzymatic synthesis. The Examiner is asked to provide a basis in fact to support the point that the determination of the rate of gluconeogenesis necessarily flows from the teachings of Goux.

Applicants respectfully submit amended Claim 20, amended as to matters of form. As such, Applicants respectfully submit that amended Claim 20 and claims depending therefrom, namely original Claims 26 and 27, are not anticipated by Goux and are in condition for allowance.

Claims Rejection – 35 U.S.C. § 103(a) – Claims 14, 15, and 18

In page 3 of the Office Action, the Examiner rejected Claims 14, 15, and 18 under 35 U.S.C. § 103(a) as being unpatentable over Landau et al. in view of Schneider (US Patent No. 6,764,817). The Office Action states:

> Landau discloses using deuterium to measure the rate of gluconeogenesis. . . Schneider teaches the functional equivalency of mass spectrometers,

> infrared spectrometers, and nuclear magnetic resonance spectrometers for the purpose of determining detecting labeled metabolite concentration and flux. Thus, given the art-recognized functional utility of these measuring means, it would have been obvious to one having ordinary skill in the art to modify Landau by using NMR in the place of mass spectrometry with the expectation of achieving suitable results.

Applicants respectfully point out that Landau does not disclose the use of deuterium to measure the rate of gluconeogenesis. Rather, Landau teaches that deuterated water, given to an individual in divided doses after fasting (14-22 hours) can provide an estimate (as a percentage) of how much gluconeogenesis contributes to total glucose production. The estimated contribution of gluconeogensis to total glucose production is not equivalent to providing a rate of gluconeogenesis; Landau only provides static data (mean+SD) by calculating the fraction of blood glucose formed by gluconeogenesis. No explicit or suggested reference to measuring a rate of gluconeogenesis is provided by Landau. As such, Landau alone or in combination with any secondary reference cannot be used to teach or suggest the use of deuterium to measure the rate of gluconeogenesis.

Applicants respectfully submit amended Claim 14, amended as to matters of form. Applicants respectfully submit that amended Claim 14 and claims depending therefrom, namely Claims 15 and 18, are patentably distinguishable over the art cited and requests their consideration and allowance.

Claims Objections –Claims 16, 17, 21-25 and 28

On page 4 of the Office Action, the Examiner objected to Claims 16, 17, 21-25 and 28 for depending upon a rejected base claim. In light of the discussions provided above, Applicants believe these objected to claims are in condition for allowance.

Applicants respectfully submit amended Claim 1, amended as to matters of form, and request entry and allowance of amended Claim 1. Applicants also respectfully submit new Claims 59-61, believed necessary to fairly protect the instant invention. Entry and allowance of new Claims 59-61 is respectfully requested

Conclusion

In light of the amendments, remarks and arguments presented above, Applicants respectfully submit that the pending and amended claims are in condition for allowance. Applicant also submits with this Amendment new claims 59-61, believed to define patentably the subject invention over the prior art of record in this Application. Applicants respectfully requests entry and allowance of new Claims 59-61. Favorable consideration for and allowance of amended Claims 1, 8, 14, 18, and 20 as well as original Claims 15-17, 19, 21-28 and new Claims 19-25 are therefore respectfully requested.

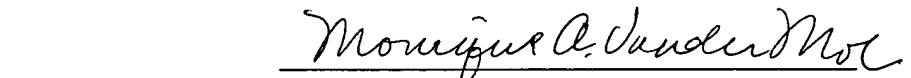
It is believed that no additional fees are due. If this is incorrect, the Commissioner is authorized to charge those fees, other than the issue fee, that may be required by this paper to Deposit Account No. 07-0153.

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: November 11, 2004

Respectfully submitted,

GARDERE WYNNE SEWELL LLP



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